

Anaphylaxis to Leuprolide Acetate Depot Injection During Treatment for Prostate Cancer

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Abstract

A 66-year-old man with clinically localized prostate cancer had elected brachytherapy as the primary management of his disease. During induction of neoadjuvant androgen deprivation for purposes of cyto-reduction, the patient experienced anaphylaxis immediately after his first injection of a leuprolide acetate depot. He required emergent intubation and extended hospitalization. Anaphylactic reactions to leuprolide acetate depots have been described as exceedingly rare. To our knowledge, we report the first case of an anaphylactic reaction to a leuprolide acetate depot injection in an American man undergoing treatment for prostate cancer.

Introduction

Since Huggins and Hodges' landmark study in 1941, androgen deprivation therapy (ADT), whether medical or surgical, has been an integral part of the management of patients with prostate cancer.¹ A variety of methods for achieving anorchid levels of testosterone are now available to the clinician. Injections of gonadotropin releasing hormone (GnRH) agonists, such as leuprolide acetate depots, are a commonly prescribed method of medical castration in the United States. These injections are usually done in the clinician's office. Anaphylactic reactions to leuprolide acetate depots have been described as exceedingly rare. To our knowledge, we report the first case of an anaphylactic reaction to a leuprolide acetate depot injection.

Case Report

A 66-year-old man with a past medical history notable for alcohol abuse, coronary artery disease, non-insulin-dependent diabetes, hypertension, and hypercholesterolemia was referred to the urologist's office secondary to an increased prostate-specific antigen level of 6.4 ng/mL. His medications included metformin hydrochloride, losartan, enalapril, and simvastatin. He had no history of allergies to medications or foods. Other than the prostate-specific antigen and an increased glycosolated hemoglobin of 9.4%, all other laboratory values were normal. Physical examination was notable for a smooth, soft, but grossly enlarged prostate gland on digital rectal examination. Biopsy was performed, revealing a Gleason 6 (3+3) prostate cancer in 1 of 6 cores.

The patient elected brachytherapy for the management of his localized prostate cancer and was referred to a radiation oncologist. Before initiation of brachytherapy, the patient was referred back to the primary urologist for neoadjuvant androgen deprivation for the purpose of reducing the gland size before treatment. Per the urologist's usual practice, the patient was started on bicalutamide 50 mg daily 3 days before appearing in the office to receive his first subcutaneous injection of 22.5 mg of the leuprolide

acetate depot. Injection proceeded in the usual fashion according to the instructions in the product insert and was performed in the left lower quadrant of the patient's abdomen.² There were no irregularities about the preparation or administration. The patient was dismissed to the waiting room for completion of paperwork and to obtain a follow-up appointment date.

Approximately 2 minutes after injection, he became acutely short of breath and complained of lightheadedness. The physician was summoned emergently and found the patient to be faint, flushed, wheezing audibly, tachypneic, and tachycardic. He was then carried by the attending urologist across the street to the emergency room by which time he was becoming cyanotic and his wheezes more faint. He was diagnosed with anaphylactic shock with acute pulmonary edema and was emergently intubated. Pharmacologic treatments, including epinephrine, diphenhydramine, famotidine, and methylprednisolone, were administered by the emergency room physicians. The patient was admitted to the intensive care unit, where he was ruled out for an acute myocardial infarction by electrocardiogram and serial troponin levels. A mild "troponin leak" (peak, 0.16 ng/mL, below the laboratory cutoff for myocardial infarction) was followed by his cardiologist back to resolution. The mild troponin leak was believed to be secondary to the stress of the respiratory distress and was not the primary inciting event. By the following day, his pulmonary edema had resolved, and he was extubated without complication. Because of the concern for recurrent anaphylaxis or respiratory distress with the depot formulation, he was maintained in a monitored setting. On hospital day 3, he was transferred to the medical/cardiac service on a telemetry ward. Subsequently, a further cardiac workup was performed. This included a cardiac catheterization that revealed his significant triple vessel disease but unchanged from previous studies. Likewise, echocardiography revealed normal left ventricular function with no new wall motion abnormalities. He remained stable without complaints and was discharged on hospital day 9 without further event. His prostate cancer management is currently on hold, with plans to return to the radiation oncologists.

Discussion

The American Brachytherapy Society has recommended use of neoadjuvant androgen deprivation for cytorreduction of large glands before receiving treatment.³⁻⁶ However, ADT has more common uses in patients with prostate cancer. Since Huggins and Hodges, ADT has been the standard of care for palliative treatment of advanced prostate cancer because most prostate cancers are, at least originally, hormone sensitive.¹ This is done surgically (via orchiectomy) or medically, via, most commonly, GnRH agonists, with or without androgen receptor blockade. Many studies have also shown survival benefits for the non-palliative adjuvant use of ADT with external-beam radiation therapy.⁷⁻⁹ Extrapolation of these data has led to the common use of ADT in conjunction with brachytherapy.

Leuprolide acetate is a commonly used GnRH agonist and is marketed by a variety of companies. As a class overall, GnRH agonists have been found safe and well tolerated. Leuprolide ace-

tate was the first GnRH agonist to be approved by the Food and Drug Administration for use in the United States in 1985, and subsequently, multiple other similar agents have been approved. Besides leuprolide acetate, other GnRH agonists approved in the United States include goserelin acetate and triptorelin pamoate. All of these formulations are given via injection by means of long acting biodegradable depot formulations.¹⁰⁻¹²

The specific leuprolide acetate depot administered to our patient was comprised of a 2-vial mechanism in which Atrigel Delivery System[®] (Poly[DL-lactide-co-glycolide and N-methyl-2-pyrrolidone]) and the leuprolide acetate are mixed immediately before injection. The delivery system has been reported to be similar to saline in frequency of adverse reactions.^{11,12} Unlike the GnRH agonist abarelix, for which anaphylaxis might occur in up to 4% of patients, anaphylaxis to depot formulations of GnRH agonists is rare.¹³

Anaphylaxis to repeated or pulsatile exposure to nondepot formulations of GnRH agonists given for male infertility or gynecologic disorders has been previously reported, though some of these reactions might have been caused by impurities in the formulations.¹⁴⁻¹⁸ As for anaphylaxis to depot preparations of GnRH agonists, there are only 2 published reports in literature, neither within the past decade. Letterie and colleagues report a woman with endometriosis who suffered recurrent anaphylaxis from a depot formulation of leuprolide acetate.¹⁹ This patient was given a 7.5-mg intramuscular dose of leuprolide acetate and 6 hours later experienced hives and then respiratory distress requiring airway management. Over the following weeks, she had recurrent bouts of hives and respiratory distress. Skin testing confirmed the allergy to the GnRH agonist. In 1994, Taylor reported an Australian patient with prostate cancer similar to our patient, who experienced an anaphylactic reaction with his first dose of leuprorelin acetate.²⁰ The patient experienced acute respiratory distress within 5 minutes of his first injection, which responded to a dose of epinephrine. Unlike the Letterie et al gynecologic patient, our patient's allergy was not confirmed with skin testing, and this is certainly a critique of our findings. However, the physical presentation, temporal relationship, and response to medication in our patient were pathognomonic for acute anaphylaxis. To our knowledge, this is the first published case report of anaphylaxis to a leuprolide acetate depot GnRH agonist in an American man during treatment for prostate cancer. Clinicians should be aware of this possibility when administering this medication.

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